

A collagen-hydrogel material, artificial lens (60) or contact lens (60) for the eye (40) fabricated from the collagen-hydrogel, which, when affixed to Bowman's membrane (48), promotes and supports epithelial cell growth (52) enabling corneal epithelium, during the healing process, to attach to and cover the lens (60) and to regenerate the stroma (50) which grows over the edge of and attaches to the optical lens (60). The collagen-hydrogel is a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked in the presence of an aqueous stock solution of collagen to form a three dimensional polymeric meshwork for anchoring collagen. The collagen-hydrogel material has a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth (52) and regeneration of the stroma (50).

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MI	Mali
AU	Australia	FR	France	MN	Mongolia
BB	Barbados	GA	Gabon	MR	Mauritania
BE	Belgium	GB	United Kingdom	MW	Malawi
BF	Burkina Faso	GN	Guinea	NL	Netherlands
BG	Bulgaria	GR	Greece	NO	Norway
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	RO	Romania
CA	Canada	IT	Italy	RU	Russian Federation
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TC	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark	MG	Madagascar		
ES	Spain				

--COLLAGEN-HYDROGEL METHODS--

5

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a collagen-hydrogel material which contains a collagen-hydrogel for promoting epithelial cell growth and which is adapted to be used to
10 fabricate artificial lens or contact lens which promotes healing of corneal epithelium during implantation and more particularly to a collagen-hydrogel biomedical material that is formed of a polymerized hydrophilic monomer which is gelled and crosslinked to form a polymeric meshwork in
15 the presence of and anchoring collagen formed of a constituent of ground tissue capable of promoting and sustaining epithelial cell growth and regenerating growth of the stroma and wherein an artificial lens, formed of the collagen-hydrogel for promoting epithelial cell growth and
20 positioned over the pupillary zone of the eye contiguous Bowman's membrane having a selected portion of corneal epithelium removed therefrom, promotes epithelial cell growth enabling corneal epithelium to attach to and cover the artificial lens to implant the same in the eye between
25 Bowman's membrane and a new layer of epithelial cells forming corneal epithelium. Laid down in the layers of the regenerated stroma are new keratocytes and collagen fibial produced from keratocytes. This invention further relates to a method for locating on a cornea an artificial lens
30 fabricated from a collagen-hydrogel for promoting epithelial cell growth and regeneration of the stroma.

2. Description of the Prior Art

Before beginning a description of the prior art, it would be helpful, in understanding the teachings of this
35 invention, to define certain of the key terms that are used in the teachings of this invention.

Collagen, in its broadest sense, is a natural protein which serves as the ground substance or adhesive substance between cells in living tissue. It is well known in the art that collagen, as a substrate material, is
5 capable of promoting cell adhesion and growth. Other proteins are also known to be capable of supporting cell growth of at least certain cell lines. In the present invention, the preferred source of collagen, as a natural protein, is derived from animal sources.

10 It is also known that other macromolecules, that is a molecule formed of a constituent of a ground substance of tissue, can support cell growth. Typical of such macromolecules, in addition to collagen, are mucopolysaccharides or fibronectin, which constituents of
15 ground substances of tissue are capable of promoting cell growth.

One class of synthetic materials which have found wide application as biomaterials is the class known as hydrogels. The term "hydrogel" refers to a broad class of
20 polymeric materials which are swollen extensively in water, but which do not dissolve in water. Generally, hydrogels are formed by polymerizing a hydrophilic monomer in an aqueous solution under conditions where the polymer becomes crosslinked so that a three dimensional polymer network is
25 formed which is sufficient to gel the solution. Hydrogels are described in more detail in Hoffman, D. S., "Polymers in Medicine and Surgery," Plenum Press, New York, pp 33-44 (1974).

Hydrogels have many desirable properties for
30 biomedical applications. For example, they can be made nontoxic and compatible with tissue. In addition, they are usually highly permeable to water, ions and small molecules. As is noted herein below, despite these favorable qualities, hydrogels have been found, in general,
35 to be unsuitable as substrates for cell attachment and growth.

With the benefit of the above described descriptions and definitions, the known prior art will now be addressed.

It is known in the art to utilize a procedure known as epikeratophakia for the correction of aphakia and high myopia in a human eye (hereinafter referred to as the Epikeratophakia Procedure"). In the Epikeratophakia Procedure, human corneal tissue is used and the corneal tissue is mechanically machined or polished to a specific lens power to form a corneal tissue lens. The corneal tissue lens is then sutured to the anterior surface of the cornea in the pupillary zone of the eye in order to change the refractive power of the eye. The specific procedure used for suturing the machined or polished corneal tissue lens to the eye requires that a portion of corneal epithelium be removed to expose a portion of Bowman's membrane and corneal tissue lens then be placed directly upon Bowman's membrane. During the healing process, corneal tissue lens is covered by epithelial cells which form the cornea epithelium implanting corneal tissue lens between Bowman's membrane and corneal epithelium. This procedure depends on the availability of human cornea tissue.

It is also known in the art to use frozen human corneal tissue, which is ground to a lenticular power, to form a corneal tissue lens and to suture the same to corneal stroma of a human eye to change the refractive power of the eye. This procedure is known as the "keratomileusis" and is described in a published article captioned "Keratophakia and Keratomileusis -Clinical Results" which appeared in August 1981, Volume 88, No. 8, at pages 709 - 715 of American Academy of Ophthalmology by Swinger, Casmir and Barraquer, Jose' (the "Swinger/Barraquer Publication").

It is also known in the art to use collagen-hydroxyethylmethacrylate hydrogels as substrates for promoting cell growth in tissue culture. The material used for the hydrogel is known as collagen-hydroxyethylmethacrylic, and referred to as a HEMA hydrogel, which was prepared in the presence of an aqueous solution of native collagen. The resulting transparent hydrogel containing collagen was evaluated as substrata for

growth of various cell lines in tissue culture. The preparation and use of collagen-hydroxyethylmethacrylate hydrogels for promoting cell growth in tissue culture is described in a article entitled USE A COLLAGEN-
5 HYDROXYETHYLMETHACRYLATE HYDROGEL FOR CELL GROWTH which appeared in Volume 77, Number 4, April 1980 at pages 2064-2068 of the Proceedings of the National Academy of Science, United States of America, wherein the authors were Linda Civerchia-Perez (the inventor herein), Barbara Faris, Gary
10 La Pointe, John Beldekas, Howard Leibowitz and Carl Franzblau (the "Civerchia Publication"). The Civerchia Publication disclosed that the collagen-hydroxyethylmethacrylate hydrogels for promoting cell growth in tissue culture were prepared by polymerizing
15 monomeric hydroxyethylmethacrylate in the presence of various concentrations of soluble native collagen. The resulting transparent hydrogels were used as substrate for growth of IMR-90 human embryonic lung fibroblasts. It was determined from these experiments that the growth of IMR 90
20 human embryonic lung fibroblasts was dose dependent upon the amount of collagen contained within the hydrogel. The resulting cell growth become intimately attached to the hydrogel substrate, and could not be removed. It was also noted during the experiments leading to the Civerchia
25 Publication that hydrogels containing albumin, gelatin (denatured collagen) or collagenase-treated collagen do not support cell growth. The results of this publication provided a foundation for a relatively easy procedure for experimentally probing mechanisms of cell adhesion and cell
30 differentiation. Substantially the same material is disclosed in United States Patent 4,565,784 wherein the inventor hereof is one of the co-inventors of the United States Patent 4,565,784.

The use of hydrogels for the correction of
35 refractive error is well known in the art, and such hydrogels are used as the base material for fabricating soft contact lens. Soft contact lens are adapted to be inserted into and removed from the eye. When soft contact lens are placed in the eye of a user, the function thereof

is to correct myopia, hyperopia, astigmatism, and aphakia. Typically such contact lens are formed of a hydrogel selected from the hydrophilic class of polymers, and the hydrogel is molded or lathed to a specific lens power. The
5 soft contact lens, when placed over the pupillary zone of the eye of a user, rests upon a tear film and corneal epithelium and function to change the refractive power of the eye.

It is also known in the art to experimentally
10 implant high water content, intracorneal implants fabricated from a Vistamarc hydrogel in the eye of rhesus monkeys and to develop keratometric data therefrom. Typical of publications describing this procedure are (i) an article captioned HYDROGEL KERATOPHAKIA: A FREEHAND
15 POCKET DISSECTION IN THE MONKEY MODEL which appeared in the 1986 Volume 70 issue, at pages 187-191 of the British Journal of Ophthalmology by Bernard E. McCarey et al (the "McCarey Publication"), and (ii) an article captioned HYDROGEL KERATOPHAKIA: A MICROKERATOME DISSECTION IN THE
20 MONKEY MODEL which appeared in the 1986 Volume 70 issue, at pages 192-198 of the British Journal of Ophthalmology by W. Houdijn Beekuis et al (the "Beekuis Publication"). These publications disclose that hydrogels can be implanted into the cornea of a monkey and that the hydrogel materials are
25 compatible with the cornea tissue of a monkey.

U. S. Patent 4,126,904 to Dennis D. Shepard, M. D. discloses artificial lenses, which are hard contact lenses, which are adapted to be placed in the eye of a user. In addition, U. S. Patent 4,126,904 discloses a
30 method of locating the same on the cornea of the eye. The disclosed artificial lens has an optical portion, which preferably is circular in shape and dimensioned to overlies the pupillary zone of an eye, and a non-optical portion, termed the "haptic" portion, which is used as a means for
35 permanently affixing the lens to the eye. As taught by U. S. Patent 4,126,904, the artificial lens can be affixed to the anterior surface of the cornea by suturing, stapling or like attachment means for securing the lens to adjacent

structure of the eyeball so that the lens will move with the eyeball.

Biologically stablized compositions comprising collagen as the major component with ethylenically unsaturate compounds used as contact lens is known in the art and are disclosed in United States Patent Nos. 4,452,925 and 4,388,428. In these compositions, the ratio of collagen by weight to the composition is very high and use of high collagen levels in contact lens may make the lens cloudy and affect the transparency thereof and are of such high levels that the same are incapable of significantly promoting epithelial cell growth and regeneration of the stroma. These United States Patents do not disclose, teach or suggest that the concentrations levels of collagen should be controlled to low levels which are capable of promoting epithelial cell growth and regeneration of the stroma.

It is also known in the art that Chiron Ophthalmics, Inc. has isolated a epithelial growth factor molecule and has used this molecule to apply to the human eye to produce a more rapid resolution of corneal abrasion.

SUMMARY OF THE INVENTION

Disclosed herein is a collagen hydrogel for promoting epithelial cell growth and regeneration of the stroma formed from a stock solution of collagen which is produced by centrifuging and concentrating a soluble collagen and adding the stock solution of collagen to a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen from the stock solution of collagen forming a collagen-hydrogel for promoting epithelial cell growth and regeneration of the stroma to produce keratocytes including collagen fibial growth, the collagen-hydrogel being capable of promoting and supporting growth of epithelial cells enabling corneal epithelium to attach to and cover the anterior surface of and to regenerate the stroma to produce

keratocytes including collagen fibial growth enabling the corneal epithelial to adhere to and cover the collagen hydrogel and to regenerate the stroma in the vicinity of the corneal epithelial, the collagen-hydrogel material
5 having a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and regeneration of the stroma.

10 Also disclosed herein is a method of fabricating a collagen-hydrogel comprising the steps of forming a radical free polymer of a hydrophilic monomer; mixing the hydrophilic monomer with a stock solution of collagen forming a clear viscous monomer solution wherein said
15 collagen-hydrogel material has a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and regeneration of the stroma; and
20 heating said viscous monomer solution in the presence of a crosslinking agent to polymerize the same into a three dimensional polymeric meshwork having collagen from the stock solution of collagen interdispersed within the three dimensional polymeric meshwork.

25 None of the prior art discloses, teaches or suggests a collagen-hydrogel which is capable of promoting epithelial cell growth when fabricated into an artificial lens which is positioned over the pupillary zone of the eye contiguous with Bowman's membrane to promote and support
30 epithelial cell growth enabling corneal epithelium to become attached to and implant the artificial lens between Bowman's membrane and corneal epithelium.

This invention relates to the use of a transparent collagen-hydrogel, as a biomedical material,
35 which is capable of being molded to a given lenticular power as in the preparation of a contact lens, to produce an artificial lens having a collagen-hydrogel for promoting epithelial cell growth. Such an artificial lens is adapted to be sutured, glued, or held in place with bandage or

therapeutic contact lens until the epithelium growth occurs directly to the anterior surface of the cornea directly on Bowman's membrane and functions to correct refractive errors of the eye. The collagen-hydrogel, referred to sometimes herein as a "collagen-hydrogel for promoting epithelial cell growth," will be covered by corneal epithelium during the healing process. The growth of the epithelial cells to form corneal epithelium on the anterior surface of the eye during the healing process is very similar to that experienced in the Epikeratophakia Procedure.

In the present invention, a hydrogel polymer is disclosed that is formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork anchoring macromolecules. The macromolecules comprise a constituent of a ground substance of tissue, such as a native collagen, interspersed within the polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth. An optical lens for the eye fabricated from the collagen-hydrogel, when attached to Bowman's membrane of the cornea of an eye, is capable of supporting and promoting epithelial cell growth enabling corneal epithelium to attach to and cover an artificial lens formed of the collagen-hydrogel for promoting epithelial cell growth during the healing process.

Also disclosed herein is an artificial lens, which preferably is a contact lens having a predetermined shape and power, which is fabricated from the collagen-hydrogel biomedical material and which is adapted to be affixed to Bowman's membrane of the cornea of an eye. When the artificial lens formed of the collagen-hydrogel for promoting epithelial cell growth is so affixed to the eye, it promotes and supports growth of epithelial cells across the surface thereof to produce corneal epithelium formed of several layers of epithelial cells. In the preferred embodiment, the contact lens comprises a lens body having anterior and posterior surface and formed of a collagen-hydrogel for promoting epithelial cell growth. The

hydrogel comprises a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork anchoring macromolecules. The
5 macromolecules comprise a constituent of a ground substance of tissue interspersed within the polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth. The collagen-hydrogel is capable of promoting and supporting growth of corneal epithelium formed of several
10 layers of epithelial cells which implant the artificial lens between Bowman's membrane and corneal epithelium. The lens body is adapted to have the posterior surface thereof positioned over the pupillary zone of the eye, and is affixed to Bowman's membrane in an area substantially equal
15 to the shape of the lens body having corneal epithelium removed therefrom. When the lens body is so affixed, it is capable of supporting and promoting epithelial cell growth enabling corneal epithelium to attach to and cover the anterior surface of the lens body.

20 Also disclosed herein is a method of fabricating a collagen-hydrogel for promoting epithelial cell growth. The method comprises the steps of forming a radical free polymer of a hydrophilic monomer; mixing the hydrophilic monomer with a diluted solution of macromolecules
25 comprising a constituent of ground substance of tissue in the presence of a weak solution of ammonium persulfate and sodium metabisulfate forming a clear viscous monomer solution; and heating the polymer mixture in the presence of a crosslinking agent to polymerize the same into a three
30 dimensional polymeric meshwork having macromolecules comprising a constituent of ground substance of tissue interspersed within the three dimensional polymeric meshwork.

The hydrogel used in the prior art for lenses
35 which are placed onto the cornea of the eye or implanted on the eye have serious disadvantages which are overcome by the teachings of this invention.

The Epikeratophakia Procedure and the procedure described in the Barraquer Publication require the use of

human corneas as the source of corneal tissue. The corneal tissue must be processed into a predetermined shape and power to fabricate an implantable corneal tissue lens. The source of human corneal tissue is limited, and the cost thereof is controlled, thereby limiting the availability of the corneal tissue for the Epikeratophakia Procedure and the use of the Epikeratophakia Procedure itself as a readily available alternative.

None of the prior art which disclose the use of collagen-hydrogel for fabricating artificial lens disclose, teach, or suggest the use of a collagen-hydrogel which has been gelled and crosslinked to form a three dimensional polymeric meshwork anchoring macromolecules wherein the macromolecules comprise a constituent of a ground substance of tissue interspersed within the polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth when the hydrogel is attached to Bowman's membrane of the cornea of an eye. As a result of collagen-hydrogel for promoting epithelial cell growth, corneal epithelium is capable of attaching to and covering the collagen-hydrogel.

The prior art Civerchia Publication discloses the experimental use of a collagen-hydroxyethylmethacrylate hydrogel as tissue growing substrate for promoting tissue cell growth of IMR-90 human embryonic fibroblasts, which are cells harvested from the lungs of a human fetus, as an experimental means to probe the mechanism of cell adhesion and cell differentiation. Thus, the teachings of the Civerchia Publication are limited to experimental tissue culture applications in that the Civerchia Publication did not recognize, teach, suggest, or disclose either the concept of or the use of a collagen-hydrogel for promoting epithelial cell growth as a basic material for fabrication of an artificial lens which, when implanted on, or into, the eye, would result in overcoming rejection of the artificial lens and the promotion of and support of the growth of epithelial cells to enable corneal epithelium to attach to and cover the anterior surface of the artificial lens with several layers of epithelial cells to form corneal epithelium resulting in the artificial lens being

implanted between Bowman's membrane and corneal epithelium.

The McCarey Publication and Beekuis Publication disclose the implantation of artificial lens, using the freepocket dissection method and the Barraquer method, respectively, wherein the artificial lenses were fabricated from hydrogels with high water content. The results disclosed by both the McCarey Publication and Beekuis Publication were that the hydrogels were well tolerated within the corneal tissue. The Beekuis Publication disclosed that the implantation of hydrogels had interface problems along the edge of implant, apparently from tissue buildup at the boundary layer between the lens/corneal epithelium interface. The Beekuis Publication noted that implants with abruptly cut edges versus a fine wedge tended to have more light scattering collagen at the implant margin. The collagen referred to is the native corneal collagen located within the corneal tissue of the monkey, and to native collagen. There is no collagen interspersed within the hydrogel molecular structure that was used to fabricate the artificial lens implanted within the monkeys as described in both the McCarey Publication and Beekuis Publication.

The artificial lens and method for implanting the same disclosed in U. S. Patent 4,126,904 relates to so called "hard contact lens", and the lens are formed of standard plastics or known hard plastics, such as polymethylmetacrylate (PMMA), none of which contain a collagen-hydrogel for promoting epithelial cell growth. The concept of surgically positioning the artificial lens over the pupillary zone of the eye is applicable to this invention, it being noted, however, that the artificial lens attached to the eye using the teachings of U. S. Patent 4,126,904 results in the lens being affixed to the anterior surface of corneal epithelium.

Thus one aspect of the present invention is that the collagen-hydrogel material for promoting epithelial cell growth can be used as the base material for fabrication of artificial lens of a reproducible power and quality as is well known in the art for producing contact

lens. The collagen-hydrogel artificial lens can be reproduced reliably in the laboratory and is not dependent upon the availability of human tissue as is the case in the production of a corneal tissue lens as described by the prior art.

Another aspect of the present invention is that the artificial lens fabricated from the collagen-hydrogel for promoting epithelial cell growth of the present invention and implanted on the eye results in the elimination of rejection of the artificial lens by the cornea and promotes and supports growth of epithelial cells during the healing process to actually implant the lens between Bowman's membrane and a new layer of corneal epithelium grown from the epithelial cells.

Another aspect of the present invention is that the artificial lens can be fabricated to any selected geometrical shape or diopter power from the collagen-hydrogel for promoting epithelial cell growth using any one of molding, lathing or freezing processes.

Another aspect of the present invention is that the collagen-hydrogel for promoting epithelial cell growth enables corneal epithelium to attach to and cover the anterior surface of an artificial lens implanted within the eye because of the growth of epithelial cells which produce a corneal epithelium having several layers of cell thickness resulting in the artificial lens being implanted between Bowman's membrane and corneal epithelium.

Another aspect of the present invention is that the implantation of the artificial lens requires only the removal of corneal epithelium from the surface of the cornea and the formation of a small "V" shaped slot and corneal wing which does not disturb the integrity of the cornea any more than a corneal abrasion or a superficial corneal laceration. The artificial lens is covered with epithelial cells during the healing process.

Another aspect of the present invention is that the necessity of maintaining a "tear layer" between the posterior surface of a soft contact lens and corneal epithelium is eliminated.

Another aspect of the present invention is that when the epithelial cells attach to and cover the anterior surface of an artificial lens fabricated from the collagen-hydrogel for promoting epithelial cell growth, if it ever becomes surgically necessary to remove and replace the artificial lens, such as for example in an accident damaging the eye, the collagen-hydrogel can be stripped from Bowman's Membrane and corneal epithelium can regrow over a defect, or a new collagen-hydrogel can be placed which will support regrowth of corneal epithelium. This is one of the basic aspects of the Epikeratophakia Procedure. That advantage is that a corneal overlay is less invasive to the eye than a corneal inlay.

Another aspect of the present invention is that the collagen-hydrogel for promoting epithelial cell growth disclosed herein is formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork anchoring macromolecules, comprising a constituent of a ground substance of tissue, which are interspersed within the polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth.

Another aspect of the present invention is that the macromolecules may be a native collagen derived from animal sources and capable of promoting and supporting growth of epithelial cells.

Another aspect of the present invention is that the sources of native collagen can be harvested from tissues of human cornea, livestock cornea or calf's or livestock skins, all of which are widely available in an almost unlimited supply and at a reasonable cost.

Another aspect of the present invention is that the hydrogel can be formed from a hydrophilic monomer such as hydroxyethyle- methacrylate.

Another aspect is that hydrogel can be polymerized in the presence of a crosslinking agent to form a three dimensional polymeric meshwork having controlled spacings between the molecules thereof to anchor the macromolecules which have a known size and to insure that

the macromolecules will be substantially uniformly interspersed within the polymeric meshwork of the polymerized hydrophilic monomer.

Another aspect of the present invention is that
5 the step of forming the crosslinking of the hydrogel can be performed with a crosslinking agent which may be external, such as for example ultraviolet radiation, or a crosslinking agent added to the hydrogel clear viscous monomer solution, which crosslinking agent may be, for
10 example, ethylene glycol dimethacrylate or methymethacrylate.

Another aspect of the present invention is that the artificial lens can be formed of the collagen-hydrogel for promoting epithelial cell growth of the present
15 invention wherein the artificial lens has an optical portion configured for placement over the pupillary zone of the eye and on the central anterior surface of Bowman's membrane of the cornea having corneal epithelium thereof removed. The optical portion of the artificial lens is
20 dimensioned to substantially cover the total anterior surface of the pupillary zone of an eye.

Another aspect of the present invention is that a method of fabricating a collagen-hydrogel for promoting epithelial cell growth which, when positioned contiguous to
25 Bowman's membrane and corneal epithelium of the cornea of an eye, promotes and supports epithelial cell growth to form a corneal epithelium is disclosed herein.

Another aspect of the present invention is that a method for locating on the cornea an artificial lens having
30 a preselected geometric shape and power and including an optical portion having an outer edge, a posterior surface and an anterior surface is disclosed herein.

Another aspect of the present invention is that the method for locating on the cornea an artificial lens
35 having a preselected geometric shape and power includes the steps of removing from Bowman's membrane over the pupillary zone of the eye a portion of corneal epithelium on an area slightly greater than the generalized shape of the artificial lens; forming on Bowman's membrane and corneal

stroma a "v" shaped annular groove having a diameter substantially equal to the maximum geometrical dimensions of the artificial lens and defining therearound a peripheral and medial edge and having a preselected depth which is less than the thickness of the corneal stroma; dissecting the peripheral edge of the groove forming a wing of corneal tissue having a preselected length; separating the medial edge of the groove from the corneal groove; placing the posterior surface of the artificial lens on the anterior surface of the cornea and positioning the outer edge of the artificial lens under the corneal wing, and affixing the artificial lens to the cornea over the pupillary zone of the eye to maintain the same on the cornea with the posterior surface in contact with Bowman's membrane and the corneal wing overlying the edge of the artificial lens enabling corneal epithelium to touch and interact with the collagen-hydrogel for promoting epithelial cell growth and to respond to the cell growth promoting constituent in the collagen-hydrogel for promoting epithelial cell growth over a healing period where epithelial cells grow over and adhere to the artificial lens implanting the same in the cornea under a new growth layer of corneal epithelium.

Another aspect of the present invention is that the artificial lens formed of a collagen-hydrogel for promoting epithelial cell growth can be implanted by using surgical procedures similar to those used in corneal overlays and corneal inlays which are easier to perform than the implantation of a lens within the corneal stroma as taught by the Swinger/Barraquer Publication.

Another aspect of the present invention is that the step of suturing the artificial lens to Bowman's membrane can be accomplished using suturing techniques presently in the art which include removable suturing material, such as nylon, mersilene, or prolene, or removable devices, such as staples, or biodegradable suturing material, such as pos, vicrylor dextron, by use of the suturing techniques disclosed in U. S. Patent 4,126,904 cited above, suturing through openings formed in the lens,

by suturing around the edge thereof by use of a running stitch suturing method known as the "running shoe lace" stitch, suturing by use of individual or "interrupted" sutures, or by use of a biodegradable adhesive which is applied to the posterior surface of an artificial lens formed of the collagen-hydrogel for promoting epithelial cell growth disclosed herein. Also, the artificial lens could be held in place with presently available "therapeutic" contact lenses.

10

BRIEF DESCRIPTION OF THE DRAWINGS

These and other advantages of this invention will be readily apparent when considered in light of the detailed description hereinafter of the preferred embodiment and when considered in light of the drawing set forth herein which includes the following figures:

Fig. 1 is a block diagram of the method for producing the collagen-hydrogel for promoting epithelial cell growth of the present invention;

Fig. 2 is a pictorial representation of an eye showing the relationship between corneal epithelium, Bowman's membrane and the corneal stroma and a representation of an artificial lens formed of the collagen-hydrogel for promoting epithelial cell growth which is adapted to be implanted with the eye using the surgical procedures set forth herein;

Fig. 3 is a pictorial representation of an eye showing the relationship between an implanted artificial lens shown in Fig. 2 implanted between Bowman's membrane and corneal epithelium after the eye has healed and the epithelial cells have grown to several layers in thickness and form corneal epithelium which is attached to and covers the anterior surface of the artificial lens;

Fig. 4 is a cross sectional view of an eye illustrating that the implanted artificial lens illustrated pictorially in Fig. 2 overlies the pupillary zone of the eye and that the same is in the form of a corneal inlay after the healing process;

Fig. 5 illustrates pictorially the first steps of the surgical procedure of removing a portion of corneal epithelium to expose a portion of Bowman's membrane and forming an annular shaped "V" groove wherein the "V" shaped
5 groove has a peripheral edge and medial edge;

Fig. 6 illustrates pictorially that the area of removed corneal epithelium is generally circular in shape and that the "V" shaped groove is located peripherally within the area of removed corneal epithelium;

10 Fig. 7 illustrates pictorially the corneal wing that is formed in the peripheral edge of the annular "V" shaped groove;

Fig. 8 illustrates the insertion of the edge of the artificial lens under the corneal wing;

15 Fig. 9 illustrates pictorially the relationship of the edge of the artificial lens under the corneal wing after completion of the surgery and before the healing process;

Fig. 10 illustrates pictorially the relationship
20 of the edge of the artificial lens under the corneal wing after completion of the surgery and after the healing process wherein the epithelial cells have grown to form corneal epithelium implanting the lens between Bowman's membrane and corneal epithelium;

25 Fig. 11 is a partial cross section showing the use of a removable suturing material for affixing the artificial lens to the cornea after the lens has been positioned in place as illustrated in Fig. 10;

Fig. 12 is a representation of a circular shaped
30 lens having two openings formed therein to permit the means for performing the suturing step illustrated in Fig. 11;

Fig. 13 is a pictorial representation of a complete eye illustrating the sutured lens on the cornea;

Fig. 14 is a representation of a rectangular
35 shaped artificial lens having an optical portion and edges which can be used to suture the lens in position over the pupillary zone of the eye;

Fig. 15 is a representation of a circular shaped artificial lens formed of the collagen-hydrogel for

promoting epithelial cell growth of this invention and having an implanted ring of material having different optical properties than that of the collagen-hydrogel for promoting epithelial cell growth and which provides
5 differential passage of an image to the retina and which is of a size and shape to be implanted on the cornea using the teachings of this invention;

Fig. 16 is a representation of a circular shaped artificial lens formed from the collagen-hydrogel for
10 promoting epithelial cell growth disclosed herein having tabs extending therefrom which may be used by a surgeon in implanting the artificial lens in the eye using the teachings of this invention;

Fig. 17 is a representation of a circular shaped artificial lens formed from the collagen-hydrogel for
15 promoting epithelial cell growth disclosed herein having two aligned circular support members extending opposite direction therefrom which may be used by a surgeon in implanting the artificial lens in the eye using the
20 teachings of this invention; and

Fig. 18 is a representation of a circular shaped artificial lens formed from the collagen-hydrogel for promoting epithelial cell growth disclosed herein having
25 three circular tabs spaced equidistantly around the periphery of an optical lens which may be used by a surgeon in implanting the artificial lens in the eye using the teachings of this invention.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The block diagram of Fig. 1 illustrates the
30 various steps of the preferred method of fabricating a collagen-hydrogel for promoting epithelial cell growth when positioned contiguous to Bowman's membrane and corneal epithelium of the cornea of an eye. The method comprises the step of forming a free radical polymerization of a
35 hydrophilic monomer which is illustrated by block 20 of Fig. 1. The so formed hydrophilic monomer solution used in the step of mixing with an aqueous solution of

macromolecules comprising a constituent of ground substance of tissue in the presence of a weak solution of ammonium persulfate and sodium metabisulfate forming a clear viscous monomer solution as illustrated by box 22 of Fig. 1. If
5 the crosslinking agent is to be used to crosslink the polymer during this step, the crosslinking agent is added during the mixing step to insure that the viscous monomer solution had a crosslinking agent therein such that the step of heating will cause the crosslinking to occur to
10 form the polymerized meshwork. The addition of the crosslinking agent to the monomer solution is illustrated by block 26 of Figure 1.

The next step of heating the viscous monomer solution is illustrated by block 28 of Figure 1. The
15 heating occurs in the presence of a crosslinking agent to polymerize the same into a three dimensional polymeric meshwork having macromolecules, which are constituent of ground substance of tissue interspersed within the three dimensional polymeric meshwork. If the crosslinking agent
20 was added to the monomer solution during the mixing step as illustrated by blocks 22 and 26, then the crosslinking and interspersing of the macromolecules with the polymeric structure occurs during the heating. By controlling the temperature and heating time of the heating step, the
25 macromolecules are substantially uniformly interspersed with the three dimensional polymeric meshwork.

Alternatively, the crosslinking can be obtained without the heating step, and without the crosslinking agent being in the viscous monomer solution, as is discussed
30 hereinbelow.

If a crosslinking agent is not added to the monomer solution during the mixing phase as described above, the crosslinking can be performed by irradiating the monomer solution during the heating phase with gamma or
35 ultraviolet irradiation. The gamma or ultraviolet irradiation causes the polymerized solution to crosslink and form a three dimensional polymeric meshwork wherein the spaces between the crosslinked molecules of the polymerized

hydrophilic monomer contain the macromolecules interspersed therein.

The collagen-hydrogel of this invention differs from those known in the prior art because of the crosslinking of the hydrogel into a three dimension meshwork for anchoring macromolecules capable of supporting anchor-dependent cell growth. Generally hydrogels per se are formed by forming a crosslinked polymer in an aqueous solution to gel the solution. This can be done by free radical polymerization of hydrophilic monomers, such as hydroxyethylmethacrylate (HEMA). This process is well known in the art and is described in Refojo, M. J. (1956), Journal Applied Polymer Science, 9, pages 3416-3426, and Holly, H. and Refojo, M. J. (1975), Journal of Biomedical Material Res., 9, page 315. Many other hydrophilic monomers in addition to HEMA can be employed.

As noted hereinabove, the preferred macromolecule added to support cell growth is native collagen, a known substrate for good cell growth. Soluble collagen can be prepared by art-recognized techniques. In addition, other proteins are satisfactory as long as they will support cell attachment and growth. One example of an additional protein known to support cell growth is fibronectin.

Macromolecules in addition to proteins can also be added to these hydrogels as long as they are capable of supporting growth of epithelial cells. Polysaccharides and mucopolysaccharides are one class of such macromolecules, and those skilled in the art will know others.

Small molecules are not employed because they can diffuse throughout the three dimensional meshwork of the crosslinked hydrogel. Since one of the requirements is that the cell growth supporting molecules must be anchored in the meshwork of the hydrogel, only macromolecules are used for promoting growth of epithelial cells. The suitable macromolecules can be water soluble or insoluble, with the former being preferred.

Hydrogel polymers formed by free radical polymerization of monomer solutions, which is the case for HEMA hydrogel, require crosslinking to form the three

dimensional polymeric structure of meshwork to gel the aqueous solution. HEMA monomer solutions normally contain some dimethacrylate which can crosslink the gel structure. The addition of crosslinking agents such as ethylene glycol dimethacrylate to the polymerization process can change the resultant hydrogel. Generally, the addition of crosslinking agents tend to increase the rigidity and mechanical strength of the hydrogel. Addition of crosslinking agents, such as ethylene glycol dimethacrylate and methymethacrylate, to the polymerization mixture in the presence of native collagen, still changes the physical properties of the hydrogel, and such additions to the polymerization mixture are compatible with the native collagen, and result in the collagen-hydrogel which support growth of epithelial cells. Other known crosslinking agents that can be used satisfactorily in producing the collagen-hydrogel include diacrylates and dimethacrylates or other divalent molecules.

The following examples are of methods for producing the collagen-hydrogel for promoting growth of epithelial cells of the present invention.

EXAMPLE I

Polymers of hydroxyethyl methacrylate (HEMA) are prepared by the method of Refojo, described hereinbefore.

Pepsin soluble collagen is prepared by stirring the ground shaved skin from a one week old calf in 0.5 M acetic acid at 4°C. The residue, after centrifugation, is resuspended in 0.5 M acetic acid containing porcine pepsin at a final enzyme-tissue ratio of 1:50 (wet weight) and allowed to stir overnight. The stabilized collagen is then precipitated by addition of solid NaCl to a concentration of 5%. The resulting precipitate is resolubilized in 0.5 M acetic acid, then dialyzed exhaustively versus 0.02 M Na_2HPO_4 , pH 7.44 at 4°C. Following dialysis, the precipitate is subjected to differential NaCl precipitation at pH 7.44 as described in Chung, E. and Miller, E.J. (1974), Science, 183, pages 1200-1201. These precipitates are then lyophilized and suspended in 0.5 M acetic acid at

a concentration of 1.2-1.4 mg/ml as determined by hydroxyproline content, and allowed to stir overnight at 4°C. The resulting solution is dialyzed against 0.15 M NaCl-0.05 M Tris, pH 7.44, overnight at 4°C. This solution
5 is used as a stock solution of collagen.

One ml of commercial HEMA, 1.0 ml of ethylene glycol, 1.0 ml of stock solution of collagen (properly diluted), 0.1 ml of 6% ammonium persulfate and 0.1 ml of 12% sodium metabisulfate are added in sequence. A
10 (quantity 0.1 ml of ethylene glycol dimethacrylate), a crosslinking agent, is added to the solution. After mixing, the resulting clear viscous monomer solution is heated for two hours at 38°C, in a mold, as used in the production of a contact lens. The resulting clear flexible
15 collagen-hydrogel is then dialyzed exhaustively versus the Tris-NaCl buffer, pH 7.44, to remove residual monomer and ethylene glycol. During dialysis, the collagen-hydrogel membranes become opaque, but transparency returns once the ethylene glycol has been exchanged for water.

20

EXAMPLE II

A collagen-hydrogel monomer viscous solution is prepared as in EXAMPLE I except that the ammonium persulfate and sodium metabisulfate are not added to the
25 solution. The collagen-hydrogel is exposed to gamma radiation or ultra violet radiation for two hours to polymerize the monomer solution. The resulting collagen-hydrogel, is sterilized in Puck's Ca⁺⁺Mg⁺⁺ free saline containing 1,000 units penicillin, 50 ml Aureomycin, and
30 0.25 ml Fungizone per ml of medium and placed under an ultraviolet light for two hours. The collagen-hydrogel is then transferred to a Puck's saline containing penicillin and streptomycin and stored at 4°C prior to use.

35

EXAMPLE III

The White Cat Study

A White Cat Study was performed on a normal cat which was white in color. The purpose of the experiment and study was to implant an artificial lens using the

teachings of the collagen-hydrogel invention into one eye of the subject cat to determine to what extent that the collagen hydrogel enhanced epithelial cell growth.

(A) Preparation of collagen hydrogel material and artificial lens from the collagen hydrogel material

The artificial lens utilized in the White Cat Study was fabricated from a collagen hydrogel material prepared in accordance with the method of Example I above.

The collagen-hydrogel material was prepared using 10 milligrams of collagen per milliliter of collagen stock solution. The collagen used was a type 8 placenta collagen. The mixture was polymerized between two glass slides to form a generally planar rectangular sheet having a thickness of about .5 millimeters to about 1.0 millimeters. One artificial lens was cut from the generally planar rectangular sheet having a generally rectangular shape. The dimensions of the artificial lens cut from the sheet of material was approximately 6 millimeters in length, approximately 3 millimeters in width and about .5 millimeters to about 1.0 millimeters in thickness. The physical characteristics of the lens were that it had the appearance of a clear plastic sheet, was smooth, transparent and optically clear.

(B) Method of surgery for affixing an artificial lens fabricated from the collagen hydrogel material to one eye of a white cat

The surgical procedure for affixing the artificial lens fabricated from the above described collagen hydrogel material to the subject white cat was performed in a standard operating room. The subject white cat was anesthetized using standard procedures. After the anesthesia became effective, the initial step performed was to remove the epithelium layer from the cornea. This step was performed by scraping off the epithelial cells located in the center of the eye forming a generally square area of about 8 millimeters by 8 millimeters. A rectangular shaped

artificial lens was prepared from the sheet of material and the dimensions of the artificial lens was approximately 6 millimeters in length, approximately 3 millimeters in width and about .5 millimeters to about 1.0 millimeters in
5 thickness.

The cornea was then prepared surgically using the steps of the method described in the connection with Figs. 5 through 9 hereof. The artificial lens was inserted under the corneal wing and sutured in place using a 10-
10 nylon suture forming 8 uninterrupted stitches. The third eyelid or nictating membrane of the subject cat was pulled over the cornea and stitched in the closed position to prevent the cat from subsequently traumatizing the eye. The subject white cat was then placed in a cat pound for a
15 period of about one week to permit the lens to become implanted by the growth of epithelial cells. After the expiration of about one week, the subject cat was sacrificed and the one eye having the artificial lens affixed thereto was surgically removed, as a nucleated eye,
20 for an eye histologic procedure.

(C) Results of eye histologic procedure of an artificial lens fabricated from the collagen hydrogel material affixed to one eye of a white cat

25 The one eye having the artificial lens affixed thereto that was surgically removed for the eye histologic procedure was placed into a standard formalin solution. The analysis of the nucleated eye was performed using standard pathological procedures for the fixation of the
30 eye. The global area of the eye disclosed that the cornea was curved, that the artificial cell was in place, that the artificial lens was clear and that the cornea was clear. An examination of a tissue sample of the cornea disclosed that the epithelial cells had grown over and implanted the
35 artificial lens. Also, it further noted that the stroma had also regenerated and had grown over the edge of and became attached to the artificial lens. The regeneration of the stroma was unexpected. The examination of the

stroma further disclosed that the eye had hematoxyalineosin present in the stroma. An examination of the layers of the stroma disclosed that new keratocytes, i.e. cells that produce collagen, were present in the laminated layers of the stroma. As a result of the presence of the keratocytes, collagen fibial, i.e. molecules produced by keratocytes, were laid down in the laminated layers of the stroma. The results clearly showed that: (a) epithelial cell growth occurred over and implanted the artificial lens into the cornea; and (b) the stroma was regenerated and the keratocytes were growing over and attaching to the edge of the artificial lens and producing collagen fibial or collagen molecules.

15

EXAMPLE IV

The Black Cat Study

The Black Cat Study was performed on a normal cat which was black in color. The purpose of the experiment and study was to implant an artificial lens using the teachings of the collagen-hydrogel invention into one eye of the subject cat to determine to what extent that the collagen hydrogel enhanced epithelial cell growth.

25

(A) Preparation of collagen hydrogel material and artificial lens from the collagen hydrogel material

The artificial lens utilized in the Black Cat Study was fabricated from a collagen hydrogel material prepared in the same manner as that described above for the White Cat Study of Example III above.

30

The sheet of collagen hydrogel material likewise had a thickness of about .5 millimeters to about 1.0 millimeters. The dimensions of the artificial lens cut from the sheet of material was approximately 6 millimeters in length, approximately 3 millimeters in width and about .5 millimeters to about 1.0 millimeters in thickness. The physical characteristics of the lens were that it had the

35

appearance of a clear plastic sheet, was smooth, transparent and optically clear.

(B) Method of surgery for affixing an artificial lens fabricated from the collagen hydrogel material to one eye of a black cat

The surgical procedure for affixing the artificial lens fabricated from the above described collagen hydrogel material to the subject black cat was substantially the same as that described hereinbefore for the white cat in The White Cat as described in Example III above. The initial step of removing the epithelium layer from the cornea was performed by scraping off the epithelial cells located in the center of the eye forming a generally square area of about 12 millimeters by 8 millimeters. A rectangular shaped artificial lens was prepared from the sheet of material and the dimensions of the artificial lens was approximately 6 millimeters in length, approximately 3 millimeters in width and about .5 millimeters to about 1.0 millimeters in thickness.

The cornea was then prepared surgically, the artificial lens was inserted under the corneal wing and sutured in situ in substantially the same manner as described above for the white cat in The White Cat Study of Example III above. The subject black cat was then placed in a cat pound for a period of about one month to permit the lens to become implanted by the growth of epithelial cells. After the expiration of about one month, the subject cat was sacrificed and the one eye having the artificial lens affixed thereto was surgically removed, as a nucleated eye, for an eye histologic procedure.

(C) Results of eye histologic procedure of an artificial lens fabricated from the collagen hydrogel material affixed to one eye of a black cat

The one eye having the artificial lens affixed thereto, that was surgically removed for the eye histologic procedure, was placed into a standard foramalin solution

and a standard pathological procedure for the fixation of the eye was performed in substantially the same manner as described above for the white cat in The White Cat Study as described above in Example III. The analysis disclosed that
5 the in the global area of the eye that the cornea was curved, that the artificial cell was in place, that the artificial lens was clear and that the cornea was clear. The examination disclosed that the eye had been subject to some trauma in that the third eyelid or nictating membrane
10 of the subject cat, which initially had been pulled over the cornea a stitched in the closed position to prevent the cat from subsequently traumatizing the eye, had been ruptured and the third eyelid permitted the cornea to be exposed in a sufficient manner for the subject black cat to
15 traumatize the eye.

However, an examination of a tissue sample of the cornea disclosed that the epithelial cells had grown over and implanted the artificial lens. Also, it further noted that the stroma had also regenerated and had grown over the
20 the edge of and became attached to the artificial lens. The examination of the stroma further disclosed that the eye had hematoxyalineosin present in the stroma and that regeneration of the stroma had also occurred in the black cat. An examination of the layers of the stroma disclosed
25 that new keratocytes, i.e. cells that produce collagen, were present in the laminated layers of the stroma. As a result of the presence of the keratocytes, collagen fibial, i.e. molecules produced by keratocytes, were laid down in the laminated layers of the stroma. The results clearly
30 showed that: (a) epithelial cell growth occurred over and implanted the artificial lens into the cornea; and (b) the stroma was regenerated and the keratocytes were growing over and attaching to the edge of the artificial lens and producing collagen fibial or collagen molecules.

35

EXAMPLE V

A collagen-hydrogel monomer viscous solution is prepared as in EXAMPLE I except that an epithelial cell growth enhancer is added to the collagen-hydrogel monomer

viscous solution before heating and polymerization. The amount of epithelial cell growth enhancer that could be added by weight could be as low as a trace of epithelial cell growth enhancer or could be in the order of the weight of collagen as determined by the ratio by weight of the collagen in the collagen-to-hydrogel weight or higher depending on the material. The maximum amount of epithelial cell growth enhancer that could be added is that amount which would make the collagen-hydrogel material cloudy and, thus impair the transparency of the collagen-hydrogel material or optical lens made therefrom. This would result in the epithelial cell growth enhancers being interspersed throughout the polymerized material.

Examples of epithelial cell growth enhancers are: (a) the epithelial growth factor molecule such as, for example an epithelial growth factor molecule isolated by Chiron Ophthalmics, Inc. and used for to produce a more rapid resolution of corneal abrasion; or (b) Fibronectin, a macromolecule which enhances epithelial cell growth.

EXAMPLE VI

A collagen-hydrogel monomer viscous solution is prepared as in EXAMPLE I. If desired, an optical lens or artificial lens can be fabricated from the collagen-hydrogel material as described herein either before or after treatment with an epithelial cell growth enhancers. Either the collagen-hydrogel material, prior to fabrication of an optical lens or artificial lens therefrom or the optical lens or artificial lens fabricated from the collagen-hydrogel material is soaked in a solution containing the epithelial cell growth enhancers in sufficient concentration to cause the molecule of the epithelial cell growth enhancers to permeate the outer layer of material forming a thin layer of epithelial cell growth enhancer on the exterior outer surface or to enable molecules of the epithelial cell growth enhancers to attach to and be supported by the outer surface of the collagen-hydrogel material.

EXAMPLE VI

The preferred embodiment of the collagen-hydrogel material for practising this invention is to prepare the collagen-hydrogel material as set forth in Example I wherein the volumes of the components comprise:

- 1 millimeter of a stock solution of collagen;
- 1 millimeter of HEMA;
- 1 millimeter of ethylenically unsaturated monomeric units;
- .1 millimeter of ammonium persulfate; and
- .1 millimeter of metabisulfate

wherein the ammonium persulfate and metabisulfate are catalysts.

(End of examples).

Based on the above examples, a calculation of the weight of collagen in the collagen-hydrogel material has a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000. This is the upper limit of the ratio by weight in that a greater ratio by weight of collagen-to-hydrogel may result in the material becoming cloudy thereby rendering the material undesirable for fabricating an artificial lens or optical lens therefrom. Thus, the collagen-hydrogel material can have a ratio by weight which is less than .6-to-1000, but at a level wherein sufficient collagen is present in weight to at least one of promote epithelial cell growth and regeneration of the stroma to produce keratocytes including collagen fibial growth.

A person skilled-in-the-art could, likewise, calculate the mole percent of each of the components in the composition.

Collagen-hydrogel which contain HEMA alone, or HEMA, ethylene glycol dimethacrylate and methymethacrylate, and all combinations thereof, in strata, support various other cell growth lines in tissue culture. Specifically,

the so formed collagen-hydrogels successfully supported growth of the following cell lines:

- (1) Rabbit smooth muscle cells;
- (2) Calf smooth muscle cell;
- 5 (3) Lung endothelial cells;
- (4) Lung epithelial cell;
- (5) Epithelial Cells; and
- (6) Regeneration of the stroma to produce keratocytes including collagen fibial growth.

10 It is likely that the collagen-hydrogel disclosed herein can serve as strata for growth of all cells of all classes, epithelial, endothelial and mesothelial, which appear to be compatible with cells of all tissues,
15 including corneal epithelial cells.

Fig. 2 illustrates pictorially the method of positioning an artificial lens, fabricated from the collagen-hydrogel as described above, and formed of a predetermined geometrical shape and lenticular power, such
20 as a contact lens, to the cornea. The eye, shown generally as 40, has a corneal epithelium 42 formed of layers of epithelial cells illustrated graphically as humps 46. Below corneal epithelium 42 is Bowman's membrane 48, which supports corneal epithelium. Below Bowman's membrane is
25 the corneal stroma 50. An artificial lens, such as for example a contact lens having an optical portion, 60 is positioned above corneal epithelium to illustrate the size thereof.

Fig. 3 illustrates pictorially the preferred
30 location of the contact lens 60 in the eye after the healing process. The contact lens 60 is located between Bowman's membrane and corneal epithelium after new epithelial cells 52 have grown during the healing process to cover the anterior surface of the lens 60.

35 Fig. 4 illustrate that the contact lens is positioned over the pupillary zone 62 of the eye and implanted between Bowman's membrane 48 and corneal epithelium 42.

Figs. 5 through 10 disclose a method for locating on the cornea an optical lens, which may be an artificial lens such as a contact lens, having a preselected geometric shape and lenticular power wherein the optical lens comprises an optical portion having an outer edge 66, an anterior surface 70 and a posterior surface 72, the elements 66, 70 and 72 being shown in Fig. 2. For purposes of the steps illustrated in Figs 5 through 10, the artificial lens has been fabricated from the collagen-hydrogel, and the specific contact lens has been formed by (i) a contact lens mold, or (ii) frozen collagen-hydrogel which has been lathed, so as to form a contact lens of a predetermined shape and power. Prior to placement of the lens on the cornea, the contact lens is sterilized by exposure to ultraviolet light.

Fig, 5 illustrates the first step of the surgical method, that step being the removing from Bowman's membrane 40, over the pupillary zone of the eye, a portion of corneal epithelium on an area slightly greater than the generalized shape of the optical lens, which area is represented by area 76. This step is similar to the removal of corneal epithelium from the anterior surface of the cornea in the Epikeratophakia Procedure.

Thereafter, the next step is that of forming on Bowman's membrane 40 a "V" shaped annular groove 78 having a diameter substantially equal to the maximum geometrical dimensions of the optical lens 60 and defining therearound a peripheral edge 80 and a medial edge 82. The "V" shaped, annular groove 78 has a preselected depth which is less than the thickness of the corneal stroma 50. Typically, the groove is formed to have a depth of about 0.3 mm, and the depth is prepared in the cornea utilizing a 7mm trephine.

Fig. 6 illustrates, by means of a front view, the cornea showing the area 76 of corneal epithelium 46 that has been removed from and to expose the area of Bowman's membrane 40 from which corneal epithelium 46 has been removed. Also, the annular shape of the "V" groove 78 is illustrated.

Fig. 7 shows the next step of dissecting the peripheral edge 80 of the groove 78 forming a wing 88 of corneal tissue having a preselected length. This step is performed by the surgeon in the following manner. As in an
5 Epikeratophakia Procedure, a corneal-spreading instrument is used to dissect the peripheral edge 80 of the groove 78 forming a corneal wing, preferably of about 1.5 mm in length. The edge 66 of the optical lens 60 is to be located under the corneal wing 88. The medial edge 82 is
10 cut free of the globe, ie. the curved surface of Bowman's membrane 40.

Fig. 8 illustrates the next step of placing the posterior surface 72 of the optical lens 60 on the anterior surface of Bowman's membrane and positioning the outer edge
15 66 of the optical lens 60 under the corneal wing 88.

Fig. 9 illustrates the final position of the lens 60 over the pupillary zone of the eye before the optical lens is attached to or affixed to the eye. The attachment can be performed in any number of procedures, one of which
20 is illustrated in Fig. 11. Fig. 9 is then a representation of the optical lens in the eye at the end of the surgical procedure, and before the healing process. It is pointed out that the anterior surface of the lens 60 is free of any cell growth. As illustrated in Fig. 9, the edge 66 of the
25 lens 60 is positioned relative to and in contact with corneal epithelium 42 and the corneal wing 88 lies flush with the anterior surface of the optical lens 60.

Fig. 10 is a representation of the condition of the eye at the end of the healing process.

30 As shown in Fig. 10, the edge 66 of the lens 60 is positioned so as to enable the epithelial cells to touch and interact with the collagen-hydrogel lens 60 to promote epithelial cell growth over a healing period. During the healing period, new epithelial cells 52 grow over and
35 adhere to the anterior surface 70 of the optical lens 60, implanting the same in the cornea under a new growth of corneal epithelium 42 formed from several layers of new epithelial cells.

Fig.11 illustrates one method of suturing a lens to Bowman's membrane wherein the optical lens includes at least two openings therein adjacent the outer edge thereof. Such a lens is illustrated in Fig. 12 as lens 90 having
5 openings 92 and 94. As illustrated in Fig. 11, the lens 90 is affixed to Bowman's membrane by the step of suturing the optical lens 90 to Bowman's membrane through the openings 92 and 94. The suture material is shown as a single loop stitch 100 in Fig. 11.

10 In the alternative, the lens 60, illustrated in Figs. 9 and 10, could be affixed to Bowman's membrane by the step of bonding with a biodegradable adhesive the posterior surface 72 of the optical lens to Bowman's membrane 40.

15 The method of affixing the lens to Bowman's membrane can be accomplished with either a removable or biodegradable suturing material, staples or the like. One preferred method for insuring that the lens 90 does not separate from Bowman's surface resulting in the edge 96
20 moving from under the corneal wing 88 is to utilize the step of suturing the optical lens 90 to Bowman's membrane with a biodegradable suturing material in the form of a running "shoe lace" stitching which passes through the outer edge of the optical lens 90 and Bowman's membrane 40.

25 Fig. 13 illustrates in a front view, after completion of locating the lens on the cornea of the eye and before beginning the healing process, the relationship of the eye 90 to the cornea wherein the lens 90, of Figs. 11 and 12, is sutured to Bowman's membrane through openings
30 92 and 94 of the lens 90.

Fig. 14 illustrates a possible lens configuration for an artificial lens 110 having an optical portion 112 configured for placement over the pupillary zone of the eye and on the central anterior surface of Bowman's membrane of
35 the cornea having corneal epithelium thereof removed. The optical portion terminates in end tabs 114 and is formed such that the optical portion is dimensioned to substantially cover the total anterior surface of the pupillary zone of an eye. The entire lens 110 including

the optical portion 112 and tabs 114 is formed of a collagen-hydrogel for promoting epithelial cell growth.

Fig. 15 is a representation of a circular shaped artificial lens 120 formed of the collagen-hydrogel for promoting epithelial cell growth and having implanted therein a ring 122 of material having different optical properties than that of the collagen-hydrogel for promoting epithelial cell growth used in the lens 120. The ring 122 functions to focus at the center thereof while the outer edge of the ring 122 passes light to the retina. This results in a differential passage of an image to the retina. The lens 120 is of a size and shape to be implanted on the cornea using the teachings of this invention.

Fig. 16 is a representation of a circular shaped optical portion 124 of an artificial lens formed from the collagen-hydrogel for promoting epithelial cell growth disclosed herein having tabs 126 extending therefrom which may be used by a surgeon in implanting the artificial lens in the eye using the teachings of this invention. The optical portion 124 and the tabs 126 are formed of the collagen-hydrogel.

Fig. 17 is a representation of a circular shaped artificial lens having an optical portion 130 formed from the collagen-hydrogel for promoting epithelial cell growth disclosed herein and two aligned circular support members 132 extending in opposite directions from the optical portion 130 which may be used by a surgeon in implanting the artificial lens in the eye using the teachings of this invention. The optical portion 130 and the tabs 132 are formed of the collagen-hydrogel.

Fig. 18 is a representation of a circular shaped artificial lens formed from the collagen-hydrogel for promoting epithelial cell growth disclosed herein wherein the optical portion 140 has three circular tabs or support members 142 having apertures formed therein spaced equidistantly around the periphery of an optical lens portion 140. The support members 142 may be used by a surgeon in implanting the artificial lens in the eye using

the teachings of this invention. The optical portion 130 and the tabs 132 are formed of the collagen-hydrogel.

It is envisioned that the collagen-hydrogel of the present invention, and artificial lens formed from the collagen-hydrogel, can be used for epicorneal, corneal or transcorneal lenses which are capable of promoting and supporting epithelial cell growth during the healing period. During the healing process, a bandage contact lens may be placed on the eye until the anterior surface of the lens is covered by corneal epithelium.

The collagen-hydrogel biomedical material disclosed herein has, in its preferred embodiment, application in the artificial lens field because of the properties of the collagen-hydrogel promoting the growth of epithelial cells. It is envisioned that such collagen-hydrogel could be used as substrata for support of growth of other cells in the human body wherein the hydrogel could be formed of any one of a number of monomers of the hydrophilic class of polymers, and that other so formed hydrogels when used in a collagen-hydrogel with appropriate macromolecules as described herein could be used to enable the growth of other classes of human tissue other than epithelial cells.

CLAIMS

1. A collagen-hydrogel for promoting epithelial cell growth comprising

5 a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen; and

10 a collagen macromolecule comprising a constituent of a ground substance of tissue interdisposed within the polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth, the collagen-hydrogel, when attached to Bowman's membrane of the cornea of an eye, being capable of at least one of supporting and promoting epithelial cells growth enabling the corneal epithelium to
15 attach to and cover the collagen-hydrogel and regeneration of the stroma, the collagen-hydrogel material having a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at
20 least one of promote epithelial cell growth and regeneration of the stroma.

2. An artificial lens for an eye which is capable of resisting rejection thereof by the cornea and supporting growth and attachment of epithelial cells from
25 the corneal epithelium to the anterior surface of and permanently implanting the artificial lens on the eye and regenerating of the stroma, said artificial lens comprising

an optical portion configured for placement over the pupillary zone of the eye and on the central anterior
30 surface of Bowman's membrane of the cornea having the corneal epithelium thereof removed, said optical portion being dimensioned to substantially cover the total anterior surface of the pupillary zone of an eye, said optical portion being formed of a collagen-hydrogel for promoting
35 epithelial cell growth and regeneration of the stroma comprising

a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen; and

- 5 a stock solution of collagen comprising a constituent of a ground substance of tissue substantially uniformly interdispersed within said polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth and regeneration of the stroma, said collagen-
- 10 hydrogel being capable of promoting and supporting growth of epithelial cells enabling corneal epithelium to attach to and cover the anterior surface of and to regenerate growth of the stroma to produce keratocytes including collagen fibial growth and to permanently implant the
- 15 artificial lens on the eye, collagen-hydrogel material having a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and
- 20 regeneration of the stroma to produce keratocytes including collagen fibial growth.

3. The collagen-hydrogel of any one of the preceding Claims wherein said collagen-hydrogel includes a epithelial cell growth enhancer.

- 25 4. The collagen-hydrogel of any one of the preceding Claims wherein said epithelial cell growth enhancer is selected to be one of fibronectin and an epithelial cell growth enhancer.

5. The collagen-hydrogel of any one of the
- 30 preceding Claims wherein said collagen macromolecule is a stock solution of collagen which is substantially uniformly distributed within the polymeric meshwork.

6. The collagen-hydrogel of Claim 2 wherein said hydrophilic monomer is one of a hydrogel monomer molecule
- 35 or hydroxyethylemacrylate.

7. The collagen-hydrogel of Claim 1 wherein said hydrogel polymer includes at least one crosslinking agent.

8. The collagen-hydrogel of Claim 9 wherein said at least one crosslinking agent is one of ethylene glycol dimethacrylate or methymethacrylate.

9. The collagen-hydrogel of Claim 1 wherein said
5 hydrogel polymer is crosslinked by means of one of ultraviolet radiation or gamma radiation.

10. The collagen-hydrogel of Claim 2 wherein said native collagen is harvested from tissues of human cornea, livestock cornea or calf's or livestock's skins.

10 11. The collagen-hydrogel of Claim 1 wherein a contact lens comprises said hydrogel, said contact lens having a predetermined shape and power which is adapted to be affixed to Bowman's membrane of the cornea of an eye and when so affixed promotes and supports growth of corneal
15 epithelial cells across the surface thereof and which is attached to the surface of the contact lens and regeneration of the stroma, said contact lens comprising

a lens body having anterior and posterior surface and formed of a collagen-hydrogel capable of promoting
20 epithelial cell growth comprising

a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen; and

25 said lens body being adapted to have the posterior surface thereof positioned over the pupil of an eye and affixed to Bowman's membrane in an area substantially equal to the shape of said lens body having the corneal epithelium removed therefrom, and when so
30 affixed being capable of supporting and promoting cell growth of the corneal epithelium which adheres to and covers the posterior surface of said lens body and regeneration of the stroma in the vicinity of the lens body.

35 12. The contact lens of Claim 11 wherein said lens body shape is molded from one of the collagen-hydrogel or from frozen and lathed collagen-hydrogel.

13. The artificial lens for an eye of any one of the preceding claims wherein the collagen-hydrogel stock solution of collagen is formed of native collagen derived from one of animal sources or mucopolysaccaria and capable of promoting and supporting growth of corneal epithelial cells and regeneration of the stroma to produce keratocytes including collagen fibial growth.

14. The artificial lens for an eye of any one of the preceding Claims wherein said native collagen of the collagen-hydrogel collagen is human tissue.

15. A collagen hydrogel for promoting epithelial cell growth and regeneration of the stroma formed from a stock solution of collagen which is produced by centrifuging and concentrating a soluble collagen and adding the stock solution of collagen to a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen from the stock solution of collagen forming a collagen-hydrogel for promoting epithelial cell growth and regeneration of the stroma to produce keratocytes including collagen fibial growth, said collagen-hydrogel being capable of promoting and supporting growth of epithelial cells enabling corneal epithelium to attach to and cover the anterior surface of and to regenerate the stroma to produce keratocytes including collagen fibial growth enabling the corneal epithelial to adhere to and cover said collagen hydrogel and to regenerate the stroma in the vicinity of the corneal epithelial, said collagen-hydrogel material having a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and regeneration of the stroma.

16. The collagen hydrogel of claim 15 further wherein said collagen-hydrogel includes a epithelial cell growth enhancer.

17. The collagen-hydrogel of Claim 15 wherein said epithelial cell growth enhancer is fibronectin.

18. The collagen-hydrogel of Claim 15 wherein said epithelial cell growth enhancer is a epithelial growth factor molecule.

19. A method of fabricating a collagen-hydrogel
5 comprising the steps of
forming a radical free polymer of a hydrophilic monomer;

mixing the hydrophilic monomer with a stock solution of collagen forming a clear viscous monomer
10 solution wherein said collagen-hydrogel material has a ratio by weight of collagen-to-hydrogel in the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and
15 regeneration of the stroma; and

heating said viscous monomer solution in the presence of a crosslinking agent to polymerize the same into a three dimensional polymeric meshwork having collagen from the stock solution of collagen interdispersed within
20 the three dimensional polymeric meshwork.

20. The method of fabricating a collagen-hydrogel of Claim 19 wherein heating is for a sufficient period of time at a selected temperature to enable the collagen to substantially uniformly interdisperse within
25 the three dimensional polymeric meshwork.

21. The method of any one of Claims 19 through 20 wherein during the step of mixing a cross-linking agent is added to the viscous monomer solution.

22. The method of fabricating a collagen-hydrogel of any one of Claims 19 through 21 wherein during
30 the step of heating the following step is performed:

irradiating the heated viscous monomer solution with ultraviolet radiation, as the crosslinking agent, to polymerize said viscous monomer solution to form said three
35 dimensional polymeric meshwork.

23. The method of fabricating the collagen-hydrogel any one of Claims 19 through 22 wherein during the step of mixing the following step is performed:

adding a epithelial cell growth enhancer to the viscous monomer solution.

24. The method of fabricating a collagen-hydrogel of Claim 23 wherein during the step of mixing the
5 following step is performed:

adding one of fibronectin or an epithelial growth factor molecule as a epithelial cell growth enhancer to the viscous monomer solution.

25. The method of Claim 24 wherein said
10 collagen-hydrogel lens is for promoting epithelial cell growth and regeneration of the stroma when positioned contiguous to Bowman's membrane and corneal epithelium of the cornea of an eye and wherein said step of mixing the hydrophilic monomer is done with a stock solution of
15 collagen comprising a constituent of a ground substance of tissue ; and

in said heating step said viscous monomer solution is heated in a mold having a predetermined shape to form a lens of a selected power to form an artificial
20 lens of a predetermined shape and power, said method further comprising the step of

freezing the crosslinked and polymerized hydrogel-collagen material in a mold having a predetermined shape to form an artificial lens of a predetermined shape
25 and power, said step of mixing the hydrophilic monomer being done in the presence of a weak solution of ammonium persulfate and sodium metabisulfate.

26. The method of fabricating a collagen-hydrogel lens of Claim 25 further comprising the step of
30 sterilizing the lens formed of the collagen-hydrogel material.

27. The method of fabricating a collagen-hydrogel lens of Claim 25 further comprising the step of
sterilizing the lens formed of the collagen-hydrogel material with an ultraviolet source of actinic
35 radiation.

28. The method of Claim 19 wherein the step of forming a radical free polymer hydrophilic monomer includes

the step of forming a radical free polymer of hydroxyethylmethacrylate.

29. The method of Claim 19 wherein said heating of said viscous monomer solution is in the presence of ethylene glycol dimethacrylate.

30. The method of Claim 19 wherein said heating of said viscous monomer is in the presence of methymethacrylate.

31. The method of Claim 25 further comprising the step of harvesting native collagen as the ground substance of tissue from tissues of human cornea, livestock cornea or calf's or livestock's skins.

32. The method of Claim 25 further comprising the step of deriving native collagen as the ground substance of tissue from animal sources which are capable of promoting and supporting growth of epithelial cells.

33. The method of Claim 25 wherein further comprising the step of deriving native collagen as the ground substance of tissue from mucopolysaccharia which is capable of promoting and supporting growth of epithelial cells.

34. The method of Claim 25 wherein further comprising the step of deriving native collagen as the ground substance of tissue from fibronectin which is capable of promoting and supporting growth of epithelial cells.

35. A method for locating on the cornea an optical lens having a preselected geometric shape and power, said optical lens comprising an optical portion having an outer edge, a posterior surface and an anterior surface, said optical lens being formed of a hydrogel polymer formed by the free radical polymerization of a hydrophilic monomer solution gelled and crosslinked to form a three dimensional polymeric meshwork for anchoring collagen; and a stock solution of collagen added to and interdisposed within said polymeric meshwork forming a collagen-hydrogel for promoting epithelial cell growth and regeneration of the stroma wherein said collagen-hydrogel material has a ratio by weight of collagen-to-hydrogel in

the range of about .6-to-1000 and less than .6-to-1000 but at a level wherein sufficient collagen is present by weight to at least one of promote epithelial cell growth and regeneration of the stroma comprising the steps of:

5 removing from Bowman's membrane over the pupillary zone of the eye a portion of corneal epithelium on an area slightly greater than the generalized shape of said optical lens;

 forming on Bowman's membrane a "v" shaped annular
10 groove having a diameter substantially equal to the maximum geometrical dimensions of said optical lens and defining therearound a peripheral edge and medial edge and having a preselected depth which is less than the thickness of the corneal stroma;

15 dissecting the peripheral edge of said groove forming a wing of corneal tissue having a preselected length;

 placing the posterior surface of said optical lens on the anterior surface of Bowman's membrane and
20 positioning the outer edge of said optical lens under said corneal wing, whereby the corneal wing lies flush with and in contact with the anterior surface of said lens; and

 affixing the optical lens to the Bowman's membrane over the pupillary zone of the eye to maintain the
25 same on the cornea with the posterior surface in contact with Bowman's membrane and the corneal wing overlying the edge of said optical lens enabling corneal epithelium to touch and interact with said optical lens formed of a stock solution of collagen added to a hydrogel polymer for
30 promoting epithelial cell growth and adherence to said optical lens and to respond to the epithelial cells growth promoting constituent in said optical lens formed of a stock solution of collagen added to a hydrogel polymer over a healing period wherein epithelial cells grow in from the
35 edge of said optical lens and over the same enabling the epithelial cells to adhere to and implant said optical lens in the cornea under a new growth of corneal epithelium formed from several layers of epithelial cells adhering to

the optical lens and the stroma has regenerated in the vicinity of the optical lens.

36. The method of Claim 35 wherein the predetermined depth of the "V" shaped groove is surgically
5 formed to be about .3mm and the predetermined length of the corneal wing is surgically formed to be about 1.5mm.

37. The method of Claim 35 wherein said optical lens includes an outer edge and wherein said steps of affixing the optical lens to the cornea comprises the step
10 of suturing the optical lens to said Bowman's Membrane.

38. The method of Claim 37 wherein the step of suturing includes the use of biodegradable sutures.

39. The method of Claim 37 wherein the step of suturing includes the use of non-biodegradable sutures.

15 40. The method of Claim 35 wherein the step of affixing the optical lens to the cornea comprises the step of bonding with a biodegradable adhesive to the posterior surface of the optical lens to the Bowman's membrane.

20 41. The method of Claim 35 wherein the step of affixing the optical lens to the cornea comprises the step of suturing the optical lens to said Bowman's membrane with a biodegradable suturing material in the form of a "running shoe lace" stitching which passes through the outer edge of said optical lens and said Bowman's membrane.

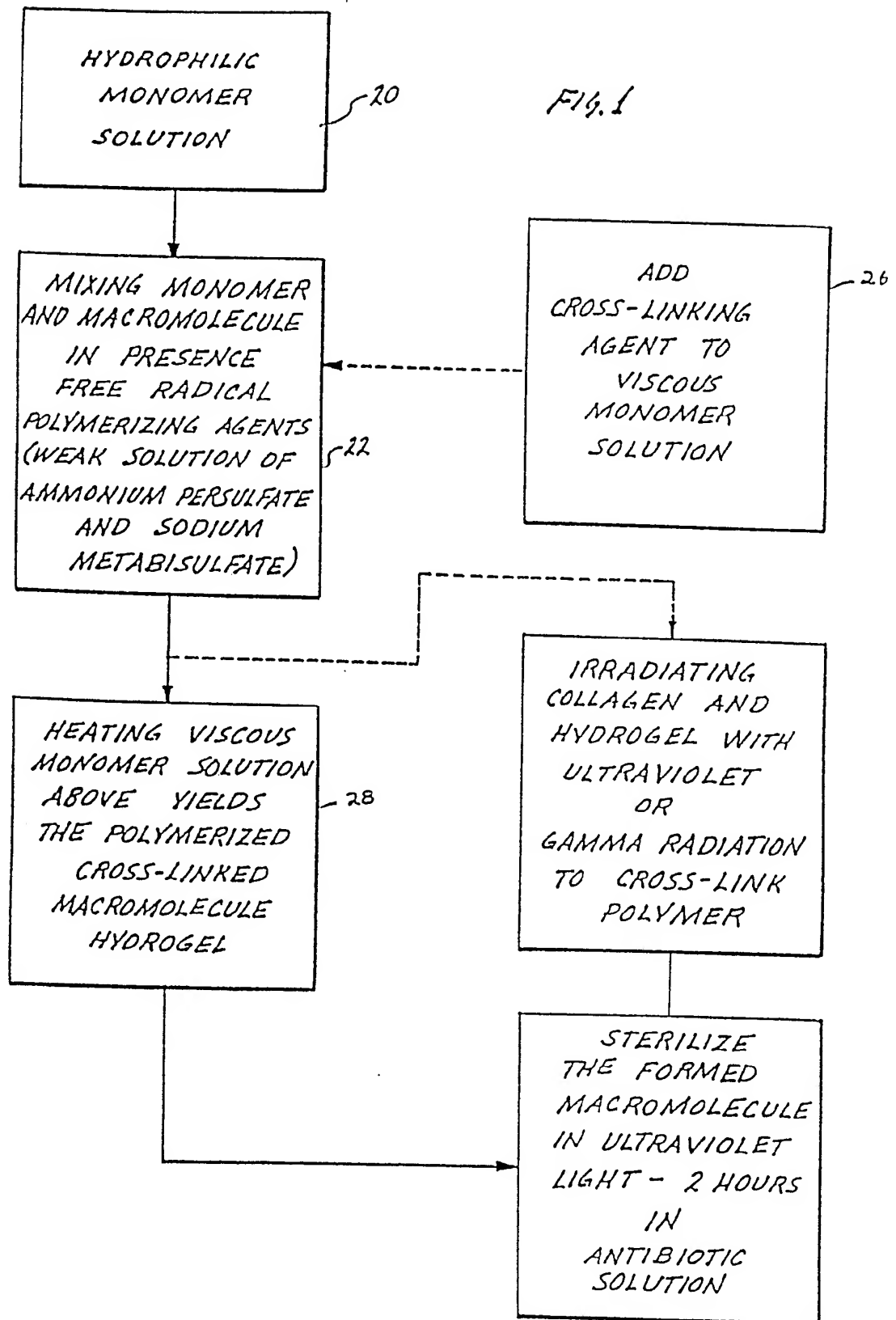
25 42. The method of Claim 35 wherein the step of affixing the optical lens to the cornea comprises the step of suturing the optical lens to said Bowman's membrane with a biodegradable suturing material in the form of an interrupted stitching which passes through the outer edge
30 of said optical lens and said Bowman's membrane.

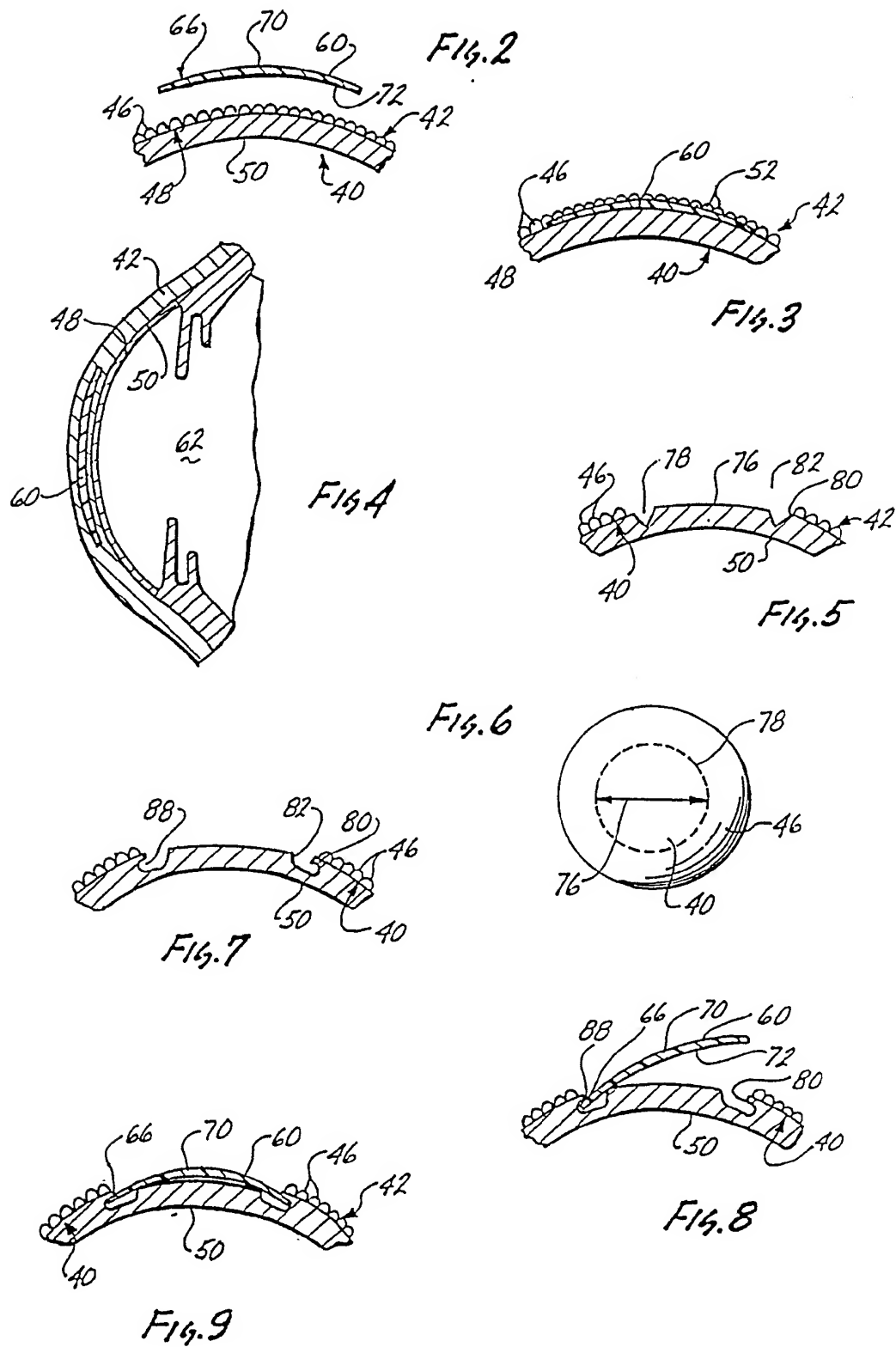
43. The method of Claim 35 wherein the step of affixing the optical lens to the cornea comprises the step of holding the lens in place under the corneal wing with a

bandage or a therapeutic contact lens until the epithelium grows over the collagen hydrogel.

44. The method of Claim 35 further comprising
the step of severing the medial edge from the curved
5 surface of the Bowman's membrane.

1/3





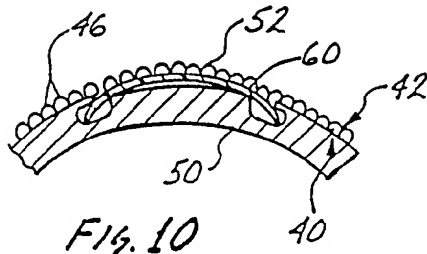


Fig. 10

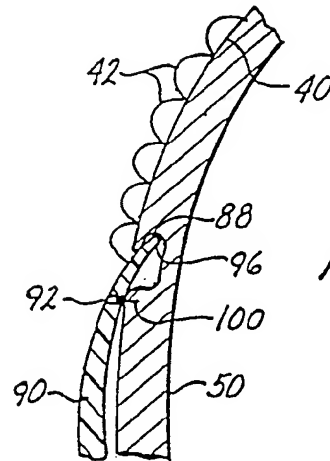


Fig. 11

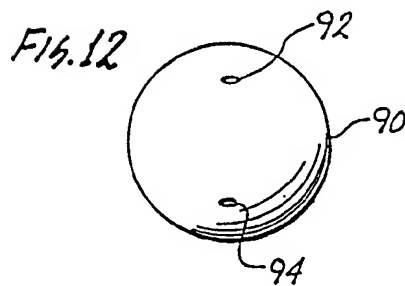


Fig. 12

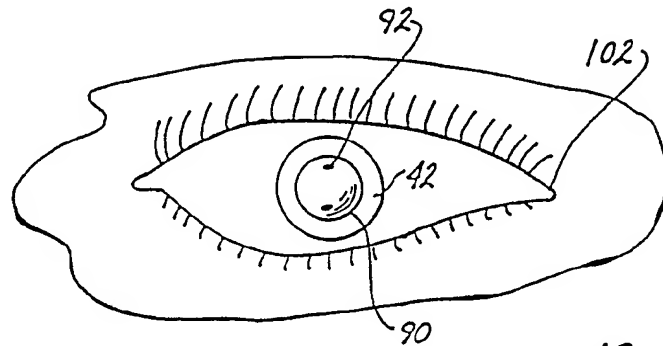


Fig. 13

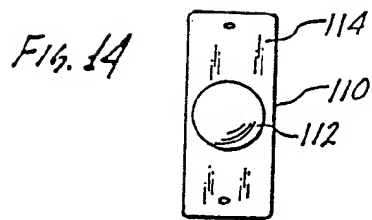


Fig. 14

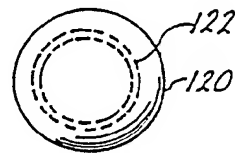


Fig. 15

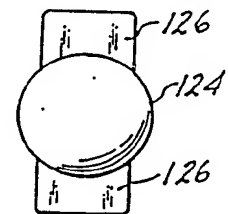


Fig. 16

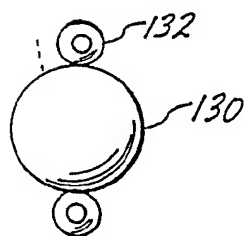


Fig. 17

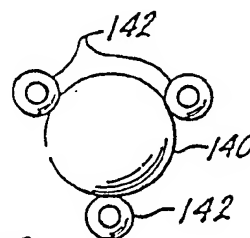


Fig. 18

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01233

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC(5): A61F 2/14; B29D 11/00		
U.S. CL.: 623/5; 264/1.7; 522/78		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	623/4,5,6; 606/107,166; 351/160R,160H; 264/1.1,1.2,1.4,1.7; 523/105,106,113,114; 522/78,87	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	US, A, 4,388,428 (KUZMA ET AL.) 14 June 1983.	1-3,6-12, 15-21,28-30, 35-44
A	US, A, 4,427,808 (STOL ET AL.) 24 January 1984.	1-3,6-12, 15-21,28-30, 35-44
A	US, A, 4,505,855 (BRUNS ET AL.) 19 March 1985.	1-3,6-12, 15-21,28-30, 35-44
A	US, A, 4,565,784 (FRANZLAU ET AL.) 21 January 1986.	1-3,6-12, 15-21,28-30, 35-44
A	WO, A, WO88/02622 (CIVERCHIA ET AL.) 21 April 1988.	1-3,6-12, 15-21,28-30, 35-44
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
28 MAY 1992		25 JUN 1992
International Searching Authority		Signature of Authorized Officer
ISA/US		RONALD L. FRINKS

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1 ☐ Claim numbers because they relate to subject matter ¹² not required to be searched by this Authority, namely:

2 ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ¹³, specifically:

3 ☒ Claim numbers 4, 5, 13, 14, 22, 23-27, 31-34 because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this international application as follows:

1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.